

JP 03-083, 926

JP 03-83926

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Translated from Japanese by the Ralph McElroy Co., Custom Division  
910 West Avenue, Austin, Texas 78701 USA

Code: 5000-72812

JAPANESE PATENT OFFICE  
PATENT JOURNAL  
KOKAI PATENT APPLICATION NO. HEI 3[1991]-83926

Int.Cl.<sup>5</sup>:A61K 31/557  
9/06  
47/10

Sequence Nos. for Office Use:

7552-4C  
7624-4C  
7624-4C

Filing No.:

Hei 1[1989]-224048

Filing Date:

August 29, 1989

Publication Date:

April 9, 1991

No. of Claims:

2 (Total of 8 pages)

Examination Request:

Not requested

## OINTMENT COMPOSITIONS

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[There are no amendments to this patent.]

Claims

1. Ointment compositions characterized by containing prostaglandin E<sub>1</sub>-inclusive esterified cyclodextrins as the active components.

2. Ointment compositions characterized by being formed from prostaglandin E<sub>1</sub>-inclusive esterified cyclodextrins as the active components, from saturated fatty alcohols, glycols, and/or absorption accelerators.

#### Detailed explanation of the invention

##### Industrial application field

This invention pertains to ointment compositions that are formed by incorporating prostaglandin E<sub>1</sub>-inclusive esterified cyclodextrins (hereafter, abbreviated as PGE<sub>1</sub>-ECD) as the active component and have excellent stability and transdermal absorption as well as drug efficacy.

##### Prior art

Prostaglandin E<sub>1</sub> (hereafter, abbreviated as PGE<sub>1</sub>) is known to have various specific pharmacological activities (for examples, blood platelet coagulation suppressing activity, peripheral vasodilation activity, etc.). Among them, peripheral vasodilation activity shows a particularly significant effect, and drug preparations having this activity are widely investigated. However, PGE<sub>1</sub> is, in general, a quite unstable compound and is easily decomposed by acids, alkali, heat or light. Particularly, it undergoes a dehydration reaction in acidic conditions or when heated and converts to prostaglandin A<sub>1</sub>. Also, it is known to undergo isomerization under alkaline conditions and converts to prostaglandin B<sub>1</sub>.

Therefore, it is strongly desirable to improve stability, especially over a long period of time, when PGE<sub>1</sub> is utilized in drug preparations to produce pharmaceuticals. As such, there are many investigations attempting to stabilize the above-mentioned unstable compound PGE<sub>1</sub>. Among them, there was the Japanese Kokai Patent Application No. Sho 59 [1984]-10525, in which it is disclosed that the stability of PGE<sub>1</sub> was significantly improved by the inclusion of PGE<sub>1</sub> with esterified cyclodextrins. It was also disclosed that it could apply to the production of pharmaceuticals of injection-type, aerosol-type, repository-type and oral-type preparations, but there was no disclosure whatsoever on ointment preparations or their drug compositions, nor were there any suggestions whatsoever of them.

##### Problem(s) to be solved by the invention

However, despite the fact that it is necessary to consider the stability of drug preparations, in particular when the unstable PGE<sub>1</sub> (showing useful pharmaceutical activity) is used as a drug component in drug preparation, there has been almost no investigation of ointment preparations for transdermal application, and the current situation is that there is no ointment preparation with satisfactory stability, transdermal absorbing properties, and drug efficacy.

### Means to solve the problem(s)

Therefore, the present inventors have conducted vigorous investigations and many studies aimed at developing PGE<sub>1</sub>-containing ointment preparations that satisfy the various aforementioned aspects. That is, based on the conditions of incorporating PGE<sub>1</sub>, and having PGE<sub>1</sub> stability over time, it was aimed at developing formulation compositions for ointment base vehicles having better stability and ointment drug formulations having good human transdermal absorption, and furthermore, the most optimum drug that can be applied as an ointment drug for treating subjects having target diseases. As a result, it was discovered that by incorporating PGE<sub>1</sub>-ECD into certain ointment base vehicles, the decomposition of PGE<sub>1</sub> was significantly suppressed, and also an ointment drug preparation having desirable performance against all the aforementioned drawbacks was obtained, achieving the present invention.

That is, the present invention is one to provide target PGE<sub>1</sub>-containing ointment compositions by incorporating PGE<sub>1</sub>-ECD in base vehicles formed from saturated fatty alcohols, glycols, and/or absorption accelerators.

To describe the present invention in more detail, the saturated fatty alcohols of the present invention are saturated fatty alcohols having 16-24 carbon atoms or a mixture of them, and are preferably saturated monohydric primary alcohols. Among them, the particularly preferred ones are cetyl alcohol, stearyl alcohol and behenyl alcohol. Additionally, the saturated fatty alcohols are incorporated at 15-45 wt% based on the total weight, and preferably at 20-30 wt%. The glycols are propylene glycol or butylene glycol (preferably 1,3-butylene glycol), and one, or a mixture of two or more, of these are utilized at 50-85 wt% based on the total weight, and preferably at 60-75 wt%. Also, in addition to the aforementioned base vehicle, it is desirable to incorporate absorption accelerators for the purpose of further promoting the absorption efficiency of transdermal absorption. As absorption accelerators, 1-dodecylazacycloheptan-2-one, 1-(2-(decylthio)ethyl)azacycloheptan-2-one, dimethyl sulfoxide, fatty alcohol such as lauryl alcohol or oleyl alcohol, crotamiton, fatty acids such as lauric acid or oleic acid, or terpenes such as 1-menthol. Among them, 1-(2-(decylthio)ethyl)azacycloheptan-2-one is the most preferred. The amount of application of the absorption accelerators is 0.01-8 wt% based on the total amount, and it is preferable that 0.1-5 wt% is incorporated.

Also, the effective component PGE<sub>1</sub>-ECD is prepared by inclusion of PGE<sub>1</sub> using the esterified cyclodextrins shown below. For examples, there are dimethyl-( $\alpha$ ,  $\beta$  or  $\gamma$ )cyclodextrins, hydroxypropyl-( $\alpha$ ,  $\beta$  or  $\gamma$ )cyclodextrins, diethyl-( $\alpha$ ,  $\beta$  or  $\gamma$ )cyclodextrins, triethyl-( $\alpha$ ,  $\beta$  or  $\gamma$ )cyclodextrins and carboxymethylethyl-( $\alpha$ ,  $\beta$  or  $\gamma$ )cyclodextrins. Among them, the  $\beta$ -type cyclodextrins are the most preferred for formulating the drug preparations. Also, among the  $\beta$  types, carboxymethylethyl- $\beta$ -cyclodextrin is the most suitable.

The amount of esterified cyclodextrin for PGE<sub>1</sub> inclusion is 1-300-fold, and preferably, 3-30-fold the amount of PGE<sub>1</sub> utilized, and using that to include 0.0001-1 wt%, but preferably 0.001-1 wt% PGE<sub>1</sub>, a better stability can be maintained for the PGE<sub>1</sub>. The amount of PGE<sub>1</sub>-ECD so obtained is 0.001-10 wt%, and preferably 0.05-5 wt%, in the formulation.

As shown above, an ointment drug preparation suitable for transdermal application and satisfying all the requirements for PGE<sub>1</sub> stability, transdermal absorption, as well as drug efficacy, can be obtained by formulating the aforementioned individual vehicle and the active component and, particularly, by preparing it with the specified formulating compositions. Additionally, other additives may be added to the ointment drug preparation of the present invention according to needs. For examples, in order to improve the stability of PGE<sub>1</sub>, organic acids (citric acid, succinic acid, tartaric acid, lactic acid, etc) and supplementary solvents (for examples, polyethylene glycols having molecular weights of 100-800, glycerol, diethylene glycol monoethyl ether, propylene glycol monomethyl ether, dipropylene glycol monoethyl ether, 2,2-dimethyl-1,3-dioxolane-4-methanol, etc.) at under 25 wt%, plasticizers (for examples, polyethylene glycols having molecular weights of 800-20,000, 1,2,6-hexanetriol, sorbitol, etc) at under 15 wt%, coupling agents (for examples, saturated fatty acids having carbon numbers of 16-24 such as stearic acid, palmitic acid and behenic acid, fatty acid amides such as oleamide, palmitamide, stearamide and behenamide, fatty acid esters having carbon number of 16-24 such as sorbitan monostearate and polyethylene glycol monostearate, and other corresponding fatty acid esters of oleic acid and palmitic acid) at under 15 wt% may be incorporated. Also, the amount of formulation of the aforementioned supplementary solvents and plasticizers is preferably 20 wt% or more for the drug preparation.

Moreover, it is preferable that, in addition to the aforementioned vehicles, antioxidants (for examples, ethylene diamine tetraacetic acid, ether chelating agents, propyl gallate, butylated oxyanisole [sic; butylated hydroxyanisole], etc), surfactants, etc. are incorporated to further improve the stability of drug preparation.

Next, in the production of the PGE<sub>1</sub>-ECD-containing ointment drug preparation of the present invention, saturated fatty alcohols (15-45 wt%), glycols (50-85 wt%), and according to needs, absorption accelerators (0.01-8 wt%), or other additives are formulated and heated to dissolve at 80-95°C and mixed in the presence or absence of nitrogen gas. The mixture is cooled while mixing at room temperature. This is followed by incorporating the inclusion product (PGE<sub>1</sub>-ECD), obtained by dissolving the active component, PGE<sub>1</sub> (0.0001-1 wt%) and the esterified ( $\alpha$ ,  $\beta$  or  $\gamma$ )-cyclodextrin (0.001-10 wt%) in an organic solvent (for examples, ethanol, methylene chloride, ethyl acetate, etc) and then distilling off the organic solvent, into the vehicle substances in the presence or absence of nitrogen gas, and after agitating and mixing, the target ointment drug preparation of the present invention can be obtained.

Application examples are carried out below to further describe the present invention more specifically.

#### Application Example 1

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol, and 0.9 g behenyl alcohol as the saturated fatty alcohols, 7.024 g propylene glycol as the glycol, and 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator, are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-carboxymethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 1 mg PGE<sub>1</sub> and 25 mg carboxymethylethyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 2

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol and 0.9 g behenyl alcohol as the saturated fatty alcohols, 0.689 g propylene glycol and 6.335 g 1,3-butylene glycol as the glycols, and 0.3 g lauryl alcohol as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-carboxymethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 1 mg PGE<sub>1</sub> and 25 mg carboxymethylethyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 3

Stearyl alcohol 0.8 g, 0.6 g cetyl alcohol and 0.6 g behenyl alcohol as the saturated fatty alcohols, 2.145 g propylene glycol and 5.005 g 1,3-butylene glycol as the glycols, and 0.8 g 1-dodecylazacycloheptan-2-one as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-carboxymethylethyl-β-cyclodextrin inclusion product, obtained by dissolving 1 mg PGE<sub>1</sub> and 49 mg carboxymethylethyl-β-cyclodextrin in ethyl acetate, and then distilling off the ethyl acetate, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 4

Stearyl alcohol 1.0 g and 0.5 g cetyl alcohol as the saturated fatty alcohols, 1.398 g propylene glycol and 5.592 g 1,3-butylene glycol as the glycols, 0.5 g PEG-6000 and 0.3 g

1,2,6-hexanetriol as the plasticizers, 0.2 g sorbitan monostearate as the coupling agent , and 0.01 g oleic acid as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-dimethyl-β-cyclodextrin inclusion product, obtained by dissolving 0.1 g PGE<sub>1</sub> and 0.4 g dimethyl-β-cyclodextrin in methylene chloride, and then distilling off the methylene chloride, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 5

Stearyl alcohol 2.5 g, 1.0 g cetyl alcohol and 1.0 g bebenyl alcohol as the saturated fatty alcohols, 3.735 g propylene glycol and 1.265 g 1,3-butylene glycol as the glycols, 0.1 g 1,2,6-hexanetriol as the plasticizer, 0.10 g polyethylene glycol monostearate as the coupling agent , and 0.27 g l-menthol as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this basic vehicle, a PGE<sub>1</sub>-triethyl-β-cyclodextrin inclusion product, obtained by dissolving 100 µg PGE<sub>1</sub> and 0.03 g triethyl-β-cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 6

Stearyl alcohol 1.50 g as the saturated fatty alcohol, 0.84 g propylene glycol and 7.56 g 1,3-butylene glycol as the glycols, and 0.05 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-carboxymethyl-β-cyclodextrin inclusion product, obtained by dissolving 10 mg PGE<sub>1</sub> and 40 mg diethyl-β-cyclodextrin in ethyl acetate, and then distilling off the ethyl acetate, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 7

Stearyl alcohol 1.0 g and 0.8 g cetyl alcohol as the saturated fatty alcohols, 6.4 g 1,3-butylene glycol as the glycols, 0.2 g sorbitan monostearate as the coupling agent, and 0.5 g PEG-6000 as the plasticizer are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-hydroxypropyl-β-cyclodextrin inclusion product, obtained by dissolving

100 mg PGE<sub>1</sub> and 1 g hydroxypropyl- $\beta$ -cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 8

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol and 0.9 g behenyl alcohol as the saturated fatty alcohols, 6.924 g propylene glycol as the glycol, 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator, and 0.1 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-carboxymethyl- $\beta$ -cyclodextrin inclusion product, obtained by dissolving 1 mg PGE<sub>1</sub> and 25 mg carboxymethyl- $\beta$ -cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 9

Stearyl alcohol 1.0 g and 0.5 g cetyl alcohol as the saturated fatty alcohols, 1.398 g propylene glycol and 5.592 g 1,3-butylene glycol as the glycols, 0.5 g PEG-6000 and 0.3 g 1,2,6-hexanetriol as the plasticizers, 0.1 g sorbitan monostearate as the coupling agent, 0.01 g oleic acid as the absorption accelerator, and 0.1 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-dimethyl- $\beta$ -cyclodextrin inclusion product, obtained by dissolving 0.1 g PGE<sub>1</sub> and 0.4 g dimethyl- $\beta$ -cyclodextrin in methylene chloride, and then distilling off the methylene chloride, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Application Example 10

Stearyl alcohol 2.5 g, 0.99 g cetyl alcohol and 1.0 g behenyl alcohol as the saturated fatty alcohols, 3.735 g propylene glycol and 1.265 g 1,3-butylene glycol as the glycols, 0.10 g 1,2,6-hexanetriol as the plasticizer, 0.10 g polyethylene glycol monostearate as the coupling agent, 0.27 g 1-menthol as the absorption accelerator, and 0.01 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-triethyl- $\beta$ -cyclodextrin inclusion product, obtained by dissolving 100 $\mu$ g PGE<sub>1</sub> and 0.03 g triethyl- $\beta$ -cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

### Application Example 11

Stearyl alcohol 1.5 g as the saturated fatty alcohol, 0.83 g propylene glycol and 7.47 g 1,3-butylene glycol as the glycols, 0.05 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator and, 0.1 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-diethylethyl- $\beta$ -cyclodextrin inclusion product, obtained by dissolving 10 mg PGE<sub>1</sub> and 40 mg diethyl- $\beta$ -cyclodextrin in ethyl acetate, and then distilling off the ethyl acetate, is added. The target ointment drug preparation is obtained with agitation and mixing.

### Application Example 12

Stearyl alcohol 1.0 g and 0.8 g cetyl alcohol as the saturated fatty alcohols, 6.0 g 1,3-butylene glycol as the glycol, 0.5 g PEG-6000 as the plasticizer, 0.2 g sorbitan monostearate as the coupling agent, and 0.5 g lactic acid as the stabilizing agent are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>-hydroxypropyl- $\beta$ -cyclodextrin inclusion product, obtained by dissolving 100 mg PGE<sub>1</sub> and 0.9 g hydroxypropyl- $\beta$ -cyclodextrin in ethanol, and then distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

### Comparative Example 1

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol and 0.9 g behenyl alcohol as the saturated fatty alcohols, 0.704 g propylene glycol and 6.345 g 1,3-butylene glycol as the glycols, and 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, 1 mg PGE<sub>1</sub> is added. The target ointment drug preparation is obtained with agitation and mixing.

### Comparative Example 2

Stearyl alcohol 0.95 g, 0.8 g cetyl alcohol and 0.9 g behenyl alcohol as the saturated fatty alcohols, 0.704 g propylene glycol and 6.320 g 1,3-butylene glycol as the glycols, and 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator are added together and heated to dissolve in an oil bath at 95°C with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, a PGE<sub>1</sub>- $\beta$ -cyclodextrin inclusion product, obtained by dissolving 1 mg PGE<sub>1</sub> and 25 mg  $\beta$ -cyclodextrin in ethanol, and then

distilling off the ethanol, is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Comparative Example 3

White vaseline 8.299 g, 0.8 g bleached beeswax, 0.3 g stearyl alcohol, 0.3 g cholesterol, and 0.3 g 1-(2-(decylthio)ethyl)azacyclopentan-2-one as the absorption accelerator are added together and heated to dissolve in an water bath with agitation. This is followed by sealing, and cooling at room temperature with agitation. To this base vehicle, 1 mg PGE<sub>1</sub> is added. The target ointment drug preparation is obtained with agitation and mixing.

#### Experimental Example 1      Stability Test

In order to investigate the stability of PGE<sub>1</sub> in the ointment drug preparations of the present invention, 2 g each of the ointment of Application Examples 1-12 and those of Comparative Examples 1-3 were filled in aluminum tubes coated on the inner side with phenol resin, and after storing for 40 days at 40°C in a constant-temperature oven, the residual amounts of prostaglandin were quantified by liquid chromatography. A column filled with octadecylsilylated silica was used for the liquid chromatography, the moving phase was a mixed solution of 0.01M KH<sub>2</sub>PO<sub>4</sub>-acetonitrile, and detection was conducted at 201 nm. The results are shown in Table 1.

Table 1

① 試 料	② PGE <sub>1</sub> 残存率 (%)
実施例 1 の軟膏製剤	89.6
実施例 2 の軟膏製剤	89.4
実施例 3 の軟膏製剤	89.2
実施例 4 の軟膏製剤	75.8
実施例 5 の軟膏製剤	78.6
実施例 6 の軟膏製剤	73.1
実施例 7 の軟膏製剤	72.1
実施例 8 の軟膏製剤	88.6
実施例 9 の軟膏製剤	85.9
実施例 10 の軟膏製剤	86.7
実施例 11 の軟膏製剤	82.4
実施例 12 の軟膏製剤	88.7
比較例 1 の軟膏製剤	44.7
比較例 2 の軟膏製剤	39.3
比較例 3 の軟膏製剤	21.6

Key: 1 Sample  
 2 Residual rate  
 3 Ointment drug preparation of Application Example  
 4 Ointment drug preparation of Comparative Example

By comparing the results of the ointment drug preparations of the present invention to those of Comparative Examples 1, 2, and 3, it was found that decomposition of PGE<sub>1</sub> was significantly suppressed by carrying out the inclusion of PGE<sub>1</sub> in esterified cyclodextrins.

### Experimental Example 2 Skin blood flow rate test

In order to confirm the localized efficacy of the ointment drug preparations of the present invention, determination of skin blood flow rate was conducted.

The compositions obtained in Application Example 1 and Comparative Examples 1 and 2 were applied openly, at 10 mg each, on a 1 x 1 cm area of the back skin of hairless mice anesthetized with urethane. The blood flow rate was determined before application and at 5 min intervals until 2 h after application, using a doppler laser blood flow meter. The differences (ml/min/100 g) before and after application were determined and used as the results, which are shown in Figure 1.

From the test results, it was found that the ointment drug preparations of the present invention showed significant increases of skin blood flow, compared to the case of Comparative Example 1, where PGE<sub>1</sub> was not included in esterified cyclodextrin, and to Comparative Example 2, where it was included in  $\beta$ -cyclodextrin; additionally, it was found that the activity was maintained until 2 h after application, showing that the ointment drug preparation of the present invention were sufficiently absorbed transdermally and exerting sufficient drug efficacy.

### Function and effect of the invention

The ointment drug preparations of the present invention are the first-ever achieved ointment compositions using the combination of PGE<sub>1</sub>-ECD and specific ointment vehicles. Additionally, as it is clear from the result of the aforementioned stability test, the decomposition of PGE<sub>1</sub> is significantly suppressed because the PGE<sub>1</sub> included in esterified cyclodextrins is formulated into the ointment base vehicles, resulting in a very desirable drug preparation. Furthermore, the drug preparations are extremely stable so that they can be stored for a long period of time, and therefore, they are desirable for quality control purposes and are suitable for product commercialization. Additionally, the skin blood flow test rate showed a significant increase of skin blood flow and it was also found that the effect could be maintained for a few hours. This sufficiently underscores the fact that the ointment drug preparations of the present invention are smoothly absorbed transdermally, which results in the expression of the drug efficacy. Thus it is desirable for formulating drug preparations.

Accordingly, the ointment drug preparations of the present invention are extremely superior in terms of stability of PGE<sub>1</sub>, expression of pharmacological activity and transdermal absorption properties. As ointment drug preparations for the purposes of local application, they can be expected to be utilized in the treatment of Raynaud's disease, decubitus, skin ulcer, psoriasis, arteriosclerosis, etc., as well as being applied as a drug for hair growth.

Particularly, that the problem of stabilizing PGE<sub>1</sub> is solved, which is the necessary condition for ointment drug preparations, is a matter of utmost importance in the drug preparation and is extremely useful to the pharmaceutical industry.

Brief description of the figure

Figure 1 shows the experimental results of skin blood flow when the drug preparations of the present invention are applied locally. The vertical axis shows the difference of blood flow rate before and after application of the compositions while the horizontal axis shows the lapsed time after application of the compositions.

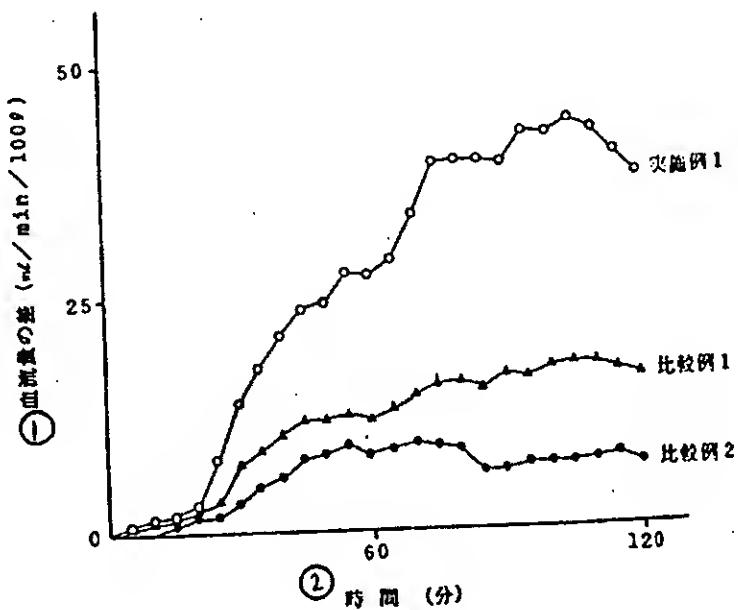


Figure 1

Key: 1 Difference in blood flow rate  
2 Time